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The role of T helper 1-cell response in *Helicobacter pylori*-infection

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ABSTRACT

Helicobacter pylori (*H. pylori*) is a human pathogen affecting over 50% of the world population. This pathogen is usually associated with chronic inflammation of the gastric mucosa that can lead to peptic ulcer disease (PUD) and gastric cancer (GC), especially in susceptible individuals. These outcomes have been attributed to the interaction of several factors, including host genetic susceptibility, local innate and adaptive immune responses, virulence factors of *H. pylori*, and environmental factors. T helper (Th) cell subsets and their signature cytokines especially IFN-γ, contribute to anti-bacterial response, but at the mean time sustaining chronic inflammatory responses in the site of infection. It has been acknowledged that *H. pylori*-infection results in a Th1-dominant response and that inflammation of the gastric mucosa depends mainly on Th1 cell responses. But, the mechanism of the role of Th1 cell responses in *H. pylori*-infection has not yet been clearly explained. In this review, we will focus on the role of Th1 involved in *H. pylori*-infection, its interaction with Th17/Treg cells and its association with the clinical consequences of the infection.

1. Introduction

Helicobacter pylori (*H. pylori*) is a microaerophilic gram-negative bacillus, spiral-shaped, flagellated bacterium which colonizes the gastric mucosa in over 50% of the world's human population [1]. *H. pylori* infection is typically acquired in early childhood. Despite triggering vigorous host innate and adaptive immune responses, *H. pylori* can persist in the human gastric mucosa for decades [2]. This bacterial pathogen plays an important role in the development of gastritis disease, peptic ulcer disease (PUD), gastric cancer (GC) and gastric mucosa-associated lymphoid tissue lymphoma (GALT) [3–6]. These different clinical outcomes have been attributed to the interaction of several factors, including virulence factors of *H. pylori*, host genetic susceptibility, local innate and adaptive immune responses, and environmental factors (e.g., high dietary salt intake, malnutrition, smoking, antioxidants, and vitamin deficiency) [7–9]. Gastric Colonization by *H. pylori* causes an inflammatory response and recruits host immune system cells such as dendritic cells (DC), macrophages, neutrophils, and lymphocytes, to the gastric mucosa [10]. The exact mechanisms by which the *H. pylori* infection induced immune response contribute to gastrointestinal mucosal damage remains to be adequately elucidated. However, many studies have demonstrated that immune response and cytokines contribute to controlling the infection and sustaining the development of the chronic inflammation [1]. Therefore, this review study was aimed to provide the most important findings about the role of Th1-mediated cytokines in different clinical expressions of *H. pylori* infection.

2. Subpopulations of T CD4 cells

T helper (Th) cells are thought to differentiate into four major $CD4^+$ functional classes, with distinct cytokine secretion phenotypes each of which elicit unique functional characteristics for each type (summarized in Fig. 1).

2.1. Th1 cells

Interleukin (IL)-12 is produced primarily by pathogen-activated antigen-presenting cells, particularly DC, macrophages, and neutrophils. IL-12 is involved in the differentiation of naive helper T cells into Th1 cells [11]. Th1 cells produce a set of cytokines including interferon gamma (IFN-γ) and IL-2 [12]. Th1 cells generate cell-mediated immunity, which is important with respect to protection against intracellular infections. Moreover, the key Th1 transcription factors are signal transducer and activator of transcription 4 (STAT4) and T-bet [13].

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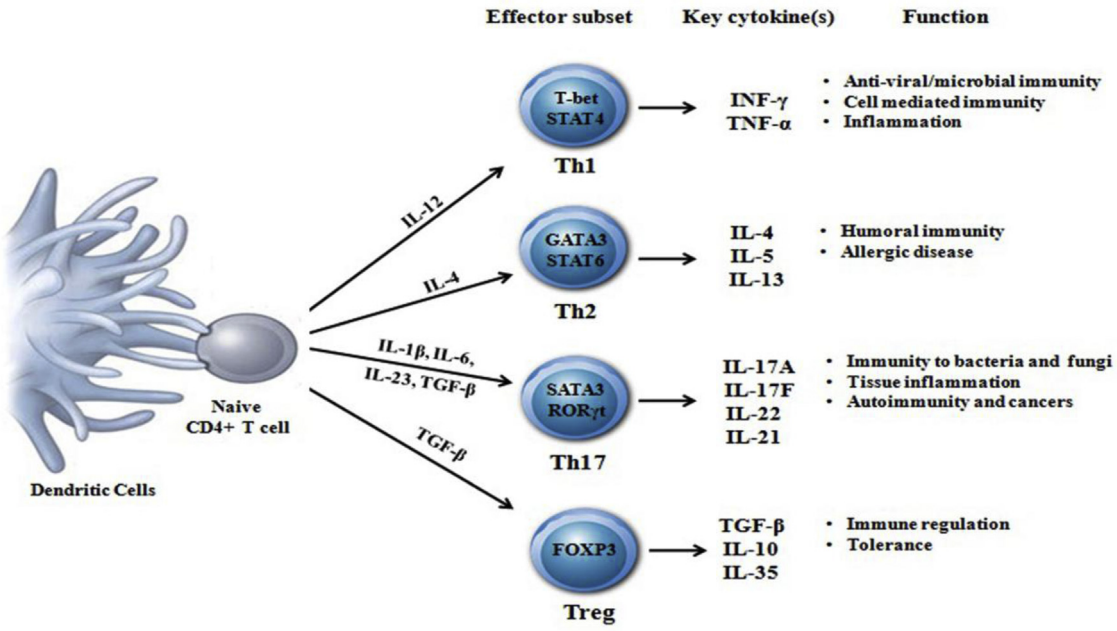

Fig. 1. Complex network of cytokines and transcription factors for generation and function of the T $CD4^+$ cell subpopulation.

2.2. Th2 cells

IL-4 is a cytokine that induces differentiation of naive helper T cells to Th2 cells. Th2 cells produce a set of cytokines including IL-4 IL-5, IL-10, and IL-13 [12,14]. Th2 responses are associated with humoral immunity and protection against intestinal helminthes. Moreover, Th2 differentiation is regulated by GATA-3 [13].

2.3. Th17 cells

The cytokines transforming growth factor beta (TGF-β), IL-1β, IL-6 and IL-23 are involved in the differentiation of naive T cells into Th17 cells in mice and humans [15]. Th17 cells have been identified as a distinct Th cell subpopulation and a novel Th lineage mediating immune response in both animal models and humans [16]. Th17 cells mainly produce IL-17 A, which could be promoted by IL-23 *in vitro* [17] and *in vivo* [18]. IL-17 A induces expression of chemokines that are neutrophil chemoattractants from epithelial cells and fibroblasts, including IL-8 [19,20]. IL-17 producing cells have been shown to be important for protection against a number of different bacterial and fungal infections [19,21]. In addition to IL-17 A, Th17 cells can secrete IL-17 F, IL-21, and IL-22 [22], which can induce massive tissue reactions by promoting the recruitment of inflammatory cells [23], while IL-22 shows specific biological properties, such as tissue repairing and wound healing [24].

2.4. Regulatory T cells (Tregs)

TGF-β is a cytokine that induces differentiation of naive helper T cells to Treg cells [25]. Tregs, formerly known as suppressor T cells, comprise a subpopulation of T cells which modulate the immune system. Tregs are usually characterized by expression of CD4, high levels of CD25, and the transcription factor forkhead box P3 (FOXP3). It is well characterized that Tregs play crucial role in maintaining self-tolerance and control of autoimmune diseases in both mice and humans [1]. Tregs depending on their maturation sites, can be divided into two subgroups, natural Tregs (nTreg) and inducible Tregs (iTreg) [26]. nTregs are developed during normal T-cell maturation in the thymus and enter peripheral tissues where they suppress the activation of self-reactive T cells [26]. The iTregs are directly developed in the peripheral lymphoid organs from naive T cells after antigen priming. Several action mechanisms by which Treg cells control the immune response have been reported: (1) inhibition by production of immunosuppressive cytokines such as IL-10, TGF-β and IL-35; (2) inhibition by cytolysis of effector cell by producing granzyme-A and granzyme-B-dependent and perforin-dependent; (3) suppression by metabolic disruption, including an inhibition of the proliferative response via IL-2 receptor, cyclic AMP (cAMP)-mediated inhibition, and CD39-and/or CD73-generated, immunomodulation mediated by the A2 adenosine receptor; (4) interaction with DC that modulates their function and maturation [27,28].

3. Virulence factors of bacterial and interaction with the host immune cell components

3.1. The cytotoxin associated gene A (cagA)

H. pylori strains are divided into two main subpopulations based on their capability to produce a 120–145-kDa immunodominant protein called the *cagA* antigen. The *cagA* gene that encodes cagA is localized at one end of the *cag pathogenicity island (cag-PAI)*, a 40 kb DNA segment that is most likely incorporated into the *H. pylori* genome through horizontal transfer state [29,30]. The cag PAI DNA segment possesses approximately 27–31 putative genes, including *cagA* and those encoding the components of a molecular syringe called type IV secretion system (T4SS), through which macromolecules are delivered from the inside to the outside of the bacterium [31,32]. The *cagL* gene, which is also located in the cagPAI, encodes the CagL protein. CagL is expressed on the surface of *H. pylori* in a T4SS-dependent manner [33].

The T4SS usually comprises a set of 12 proteins (VirB1-11 and VirD4), of which VirD4 (HP0524) acts as a *coupling* protein that recruits substrates to the T4SS apparatus. The *H. pylori* VirD4 acts as an adaptor protein for the transfer of the CagA protein and possibly other unknown proteins into the host cells [34]. Upon the attachment of cagA-positive *H. pylori* to the gastric epithelial cell, the CagA protein is injected directly into the cell [35]. Upon injection, unphosphorylated CagA interacts with host cell proteins. This causes dysregulation of epithelial structure and integrity through its effect on host cell signaling and induction of pro-inflammatory and mitogenic responses [36–38].

CagA is not only injected into gastric epithelial cells but also injected into B lymphoid cells and murine and human DCs [39–41].

Remarkably, CagA translocation into DCs suppresses host immune response by reducing the secretion of pro-inflammatory cytokines such as IL-12p40 and enhancing the expression of the suppressive cytokine IL-10. This indicates a dual pro- and anti-inflammatory role for CagA during *H. pylori* infection which is dependent on the cellular context [41,42].

More recent data have demonstrated rapid maturation and activation of monocyte-derived DCs by intact *H. pylori* [43,44]. DC activation is accompanied by expression of high levels of IL-12 and low levels of IL-10, which should favor a Th1-type T-cell response. *In vitro* study by guiney et al. suggested that the products of the *cag* pathogenicity island may be involved in the activation of IL-12 expression because IL-12 expression is reduced by 50% when an isogenic *cagE* mutant is used [43]. Another factor, which may be involved in IL-12 induction, includes products of the genes in the *H. pylori* plasticity region [45], a region of the genome with substantial strain variation.

In addition, *H. pylori*-pulsed DCs cause activation of naive autologous T cells and expression of IL-2, tumor necrosis factor alpha (TNF-α), and IFN-γ but not IL-4 [44]. These data indicate that *H. pylori* virulence factors influence DC activation and maturation in a way that Th1 polarization is driven. This data might explain, at least in part, the Th1 polarization observed in the gastric mucosa of *H. pylori*-infected individuals.

3.2. The vacuolating cytotoxin A (vacA)

The vacA gene, which is an important *H. pylori* virulence factor present in all strains, and encodes an 87 kD protein. The initial studies on vacA have detected two main polymorphic regions including the signal sequence (s1 and s2) and two middle regions (m1 and m2). However, the more recently studies have identified two intermediate regions (i1 and i2) which are located between the s and m regions [46]. The mosaic combination of s and m region allelic types determines the production of the cytotoxin and is associated with pathogenicity of the bacteria [47].

VacA is considered a *H. pylori* toxin with multiple cellular effects in various host cell types. The toxin inserts into the cell membrane and forms anion-conducting channels. This seems to be important for the modulation of other vacA activities including the ability to induce large acidic vacuoles, which is the first epithelial cell phenotype attributed to the toxin [48–50]. The VacA toxin interferes with autophagy pathways of gastric cells, causes gastric epithelial erosions in mice, induces cell apoptosis, and causes cell necrosis. It also has immunomodulatory properties by inhibiting T- and B-lymphocyte proliferation and activation [7,51]. VacA, through an unknown mechanism, has also an indirect effect on T cells. It can induce DC tolerance and regulatory T cell induction; however, this effect has not yet been documented in human cells [52,53]. VacA also induces a proinflammatory effect on T cells that is mediated by activation of NF-kB and leads to upregulation of IL-8 [54].

3.3. The H. pylori neutrophil-activating protein (HP-NAP)

The gene, napA, encoding the neutrophil-activating protein of *H. pylori* (HP-NAP, or denoted as NapA) has been detected in all *H. pylori* isolates from infected patients. *H. pylori*-NAP is classified as a protein virulence factor of *H. pylori* that can stimulate neutrophils to generate reactive oxygen species (ROS) when this pathogen adheres to endothelial cells. This 17-kDa protein is known as a major antigen in the human immune response to *H. pylori*-infection [55]. *H. pylori*-NAP through binding to both neutrophil glycosphingolipids and mucin, can mediate neutrophil adhesion to endothelial cells [56] and play an important role in recruiting human monocytes and neutrophils to the site of *H. pylori* infection [57,58].

The role of *H. pylori*-NAP in triggering cell-mediated immune response has also been shown before [59–61]. It has been shown that *H. pylori*-NAP can induce the innate immune cells including monocytes and neutrophils to produce IL-23 and IL-12 and elicit an antigen-specific Th1-polarized T-cell response in the gastric mucosa of *H. pylori*-infected patients [59–61]. In this context, *H. pylori*-NAP induces monocytes to express IL-23 and to differentiate into DC [60]. Moreover, it stimulates macrophages to express the MHC-II [62]. Thus, *H. pylori*-NAP is expected to be capable of promoting the induction of Th1 cell responses in *H. pylori*-infected patients. Furthermore, addition of *H. pylori*-NAP into culture of T cell lines, as an immune modulator, resulted in a remarkable increase in the number of IFN-γ producing T cells and in adverse, decrease of IL-4 secreting cells. Thus, *H. pylori*-NAP promotes shifting the cytokine profile of antigen-activated human T cells from Th2 to a Th1 cytotoxic phenotype [60].

Induction of the Th1 cell response by *H. pylori*-NAP may also contribute to the pathogenesis of *H. pylori* infection. The models of how *H. pylori*-NAP exerts its pathological effects by secreting pro-inflammatory cytokines, promoting leukocyte recruitment, and subsequently stimulating its immunomodulating activity have been well clarified in the other reviews [63].

4. The role of macrophages in induction of Th1 cell responses in *H. pylori*-infection

Macrophage activation is a critical constituent of the host immune response to *H. pylori*-infection [64]. There are different types of macrophages including M1 (inflammatory macrophages), M2 (remodeling/fibrotic), and Mreg (resolving/immune-regulatory) [65]. The M1 macrophages are characterized by proinflammatory cytokines (such as TNF-α and IL-6) secretion and production of nitric oxide (NO) synthase (NOS). Activation of M1 macrophages can result in an effective pathogen killing mechanisms [65,66]. Alternatively, activated M2 macrophages are specialized for responses to parasites and wound healing, with enhanced expression of resistin-like molecule alpha (RETNLA), arginase 1 (ARG1), and chitinase 1 (CHIA1) [65]. The M2 macrophages are also referred to as tumor-associated macrophages, given their angiogenic and chemotactic stimuli and tumorigenic properties [67]. The Mreg macrophages secret high levels of anti-inflammatory cytokines like IL-10 and TGF-β (Fig. 2) [65,66]. Recent studies have shown that *H. pylori* infection most often results in M1 and Mreg macrophage activation [68,69]. It has been shown that Macrophages respond to *H. pylori*-derived products and signals from gastric epithelial cells, which are in direct contact with the bacterium. Available data suggest that recruited macrophages and monocytes in the site of infection can produce IL-12, by which stimulate Th1 cells and result in production of cytokines such as IFN-γ [70,71].

5. Th1-cells, cross talk with Th17 and Tregs, and induction of gastritis

Because most infected patients with *H. pylori* are unable to clear the pathogen, it has been suspected that *H. pylori* may somehow hamper the host immune response. Several *H. pylori* virulence factors such as vacA toxin may interfere with protective immunity by acting on professional antigen-presenting cells (APCs) impairing their antigen processing capability and subsequently modulating immune response to *H. pylori* infection [72]. The failure to clear *H. pylori* infection from the gastric mucosa almost invariably leads to chronic gastritis in infected patients. Gastritc colonization of *H. pylori* infection in human is followed by gastric mucosal inflammation, which varies depending on the host immune response against this bacterium [73]. In infected patients, *H. pylori* virulence factors such as NAP, VacA cytotoxin or CagA protein, and urease are allowed to cross the damaged layer of gastric cells and to induce chemotaxis and activation of human neutrophils and monocytes. For example, *H. pylori*-induced CXCL8/IL-8 production by gastric epithelial cells plays a central role in the initial host immune response to this bacterium; because IL-8 is a strong chemotactic and activating

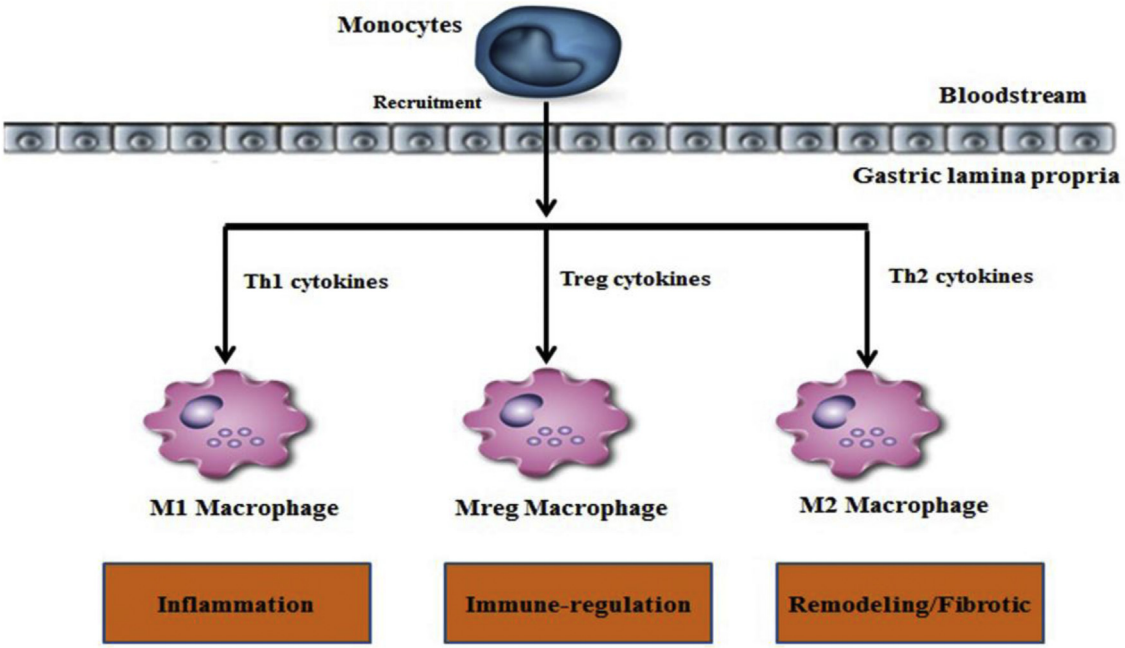

Fig. 2. The role of $CD4^+$ T-cell subpopulations derived cytokines in generation of macrophage subpopulations and consequences of their activation.

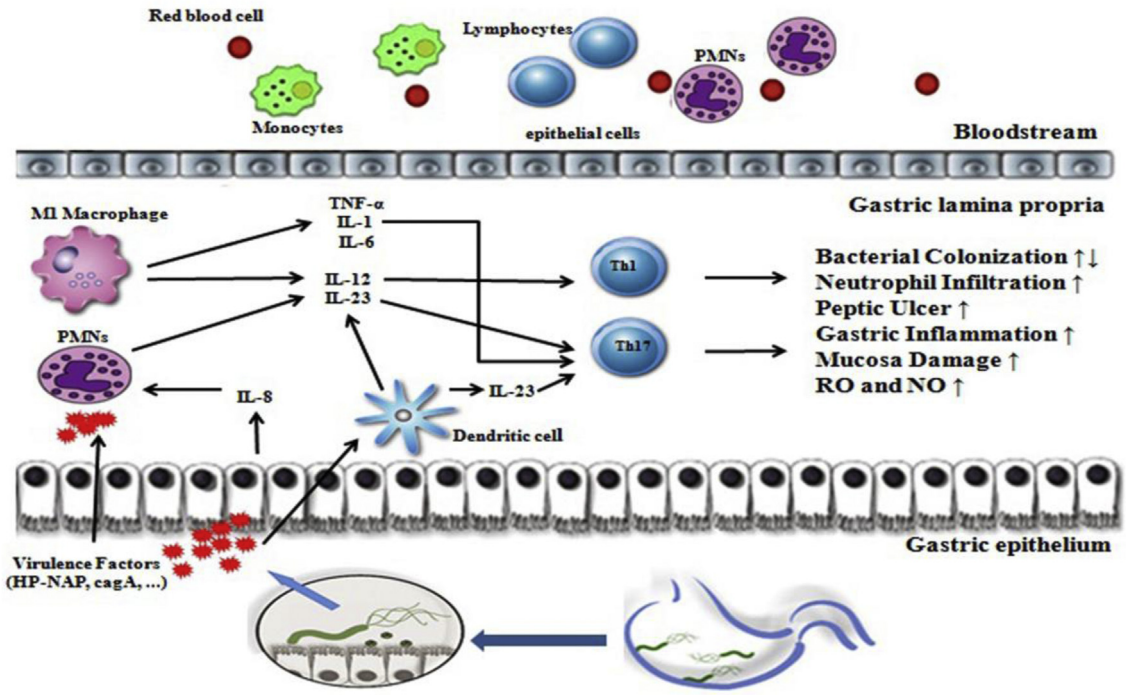

Fig. 3. *Helicobacter pylori,* its interaction with immune cells, and immune pathogenesis of gastric mucosa damage. Virulence factors of *H. pylori* activate the innate immune system cells (neutrophil, dendritic cells (DCs) and M1 macrophage) in gastric mucosa of infected patients. Activation of neutrophil, DC and M1 macrophage can lead to important antimicrobial effects but can also result in inflammation and tissue injury due to release of inflammatory mediators such as TNF-α, IL-8, IL-6, IL-12 and IL-23, reactive oxygen species (ROS), and nitric oxide (NO). The release of inflammatory mediators induces the preferential development of *H. pylori*-specific Th1/Th17 cell responses. Reactive oxygen (RO) and NO species from neutrophils and M1 macrophage cells increase the oxidative stress that together with other immune-mediated mechanisms, induce apoptosis of the epithelium. In addition, oxidative stress can damage DNA, leading to the disruption of gene function. Thus, the longer the period of exposure of a tissue to activated immune/inflammatory cells and mediators, the more cellular damage may accumulate.

factor for neutrophils, which in turn contribute to increasing the inflammatory response [74]. When macrophages are recruited to sites of infection and exposed to inflammatory stimuli, they secrete cytokines, such as IL-1, IL-6, TNF-α, IL-12, IFN-γ, and chemokines, such as IL-8 (Fig. 3). Recruited neutrophils in gastric mucosa can also produce IL-12 in response to bacterial antigens [75]. This is an essential step in the natural history of infected patients with *H. pylori*, because the local cytokine *milieu*, particularly IL-12 produced by neutrophils and macrophages of the natural immunity, is essential to drive the subsequent specific $CD4^+$ T-cell response into a more or less Th1-polarized immune response (Fig. 3). $CD3^+CD4^+$ T cells increase in gastric lamina propria (LP) of patients infected with *H. pylori* and play important roles in the

pathogenesis of persistent infection [76,77]. Studies of host immune responses to *H. pylori* infection have mainly focused on Th1, Th17, Th2 and Treg cells [1,2,78], and as mentioned before, it is usually acknowledged that *H. pylori* infection results in a Th1-dominant immune response and that gastric inflammation mainly depends on Th1 cell immune responses [76,79]. Previous studies have shown that expression of IL-6, IL-23, IL-12 and TGF-β is elevated in the gastric mucosa of patients with *H. pylori* infection [43,80–82]. Theis secretion of IL-6, IL-23, IL-12 and TGF-β creates a cytokine milieu that facilitates the polarization of Treg and Th1/Th17 cells response to *H. pylori* infection. Both Th1 and Th17 immune responses mediate mucosal inflammation in infected patients with *H. pylori* (Fig. 3). In terms of the dynamics of T $CD4^+$ helper cell immune responses, it has been demonstrated that at the early stage of infection Th17 cell responses are induced earlier than Th1 cell responses, indicating that Th17 and Th1 cells may promote gastric mucosal inflammation at different stages. Currently, the relationship between Th1 and Th17 cells in *H. pylori* infection is not exactly clear. A study on mice model of *H. pylori* infection has demonstrated that Th1 cell responses to *H. pylori* infection are significantly reduced in IL-17 knockout mice but the responses are not significantly different between the IL-17 blockade and IL-17 overexpression models. The inconsistency in the results regarding IL-17 knockout and IL-17 blocking model might be due to IL-17 activity not being absolutely blocked when anti-IL-17 is used. These results have proposed that the Th17/IL-17 pathway modifies Th1 cell responses, and Th1 and Th17 cell responses may act synergistically to induce gastric mucosal inflammation during *H. pylori* infection [83]. A study with mice model of *H. felis* infection also has shown that neutralization of IFN-γ significantly reduces the severity of gastric mucosal inflammation, which strongly supporting the concept that preferential long-lasting activation of a Th1 cell responses contributes to progress and maintenance of gastric pathology [84].

Recent studies have shown that Tregs suppress the immune response to *H. pylori* infection [85,86]. Accumulating evidence indicates that the failure of the host to eradicate *H. pylori* may be due to the ability of the pathogen to evade T cell immunity by inducing Tregs. Recent studies have also shown that *H. pylori*-specific Tregs suppress memory T-cell responses in infected patients [87,88]. Studies in mice infected with *H. pylori* have shown that depletion of Tregs leads to increased gastric inflammation and reduced colonization of *H. pylori* infection [85]. These findings suggest that Tregs contribute to the persistence of *H. pylori* colonization in gastric mucosa. A study has confirmed that the number of Tregs and the expression of IL-10 and TGF-β1 are significantly higher in infected patients than in uninfected subjects. Moreover, the number of Tregs and the expression of IL-10 and TGFβ1 are significantly higher in infected patients with gastritis than in infected patients with PUD [89], strongly supporting the concept that Treg cell responses in infected patients with gastritis are capable of modulating Th1 and Th17 cell responses that possibly contribute to the persistence of *H. pylori* infection.

6. Th1-cells and peptic ulcer disease (PUD)

Infection of the gastric antrum by *H. pylori* represents a key factor in the etiology of various gastrointestinal diseases, but the reason why only a limited number (10–20%) of infected patients with *H. pylori*-induced PUD undergo complications of the infection remains to be clarified. *H. pylori* infection itself can induce mucosal damage, and some mechanisms of gastric mucosal damage may be correlated with the virulence factors of *H. pylori* [90]. *H. pylori* and its antigens, such as VacA, NAP or CagA, induce gastric epithelial cells to produce IL-8 [91–93]. *H. pylori* activates macrophages, and triggers IL-18, IL-12, and IL-17 production [7,21,94]. IL-18 and IL-12 induce the preferential development of *H. pylori*-specific Th1 cell responses. The T $CD4^+$ cell response polarizes more into the Th1 pattern with autocrine secretion of IFN-γ [95]. TNF-α and IFN-γ secreted by chronically activated *H. pylori*-specific $CD4^+$ Th1 may lead to PUD because TNF-α and IFN-γ are able to induce functional alterations of gastric epithelial cells, and following increased gastric acid secretion (Fig. 3) [96].

Recent studies have shown that Th1 polarization of *H. pylori*-specific T cell is related to more severe disease in infected patients [97–99]. The theory that the Th1-type of gastric T cell response against *H. pylori* infection contributes to the pathogenesis of PUD is indirectly supported by an intersting observation that, in spite of a high frequency of *H. pylori* colonization, PUD and active gastritis were almost absent in renal allograft recipients undergoing strong T cell immunosuppression therapy [100]. In agreement with above results, a recent study has demonstrated that the frequencies of IL-17 A^+ and IFN-γ^+ cells are significantly higher in antrum biopsies of gastric ulcer (GU) patients compared to *H. pylori*-infected non-ulcer dyspepsia patients. In addition, IL-17 A^+ and IFN-γ^+ cells are not detected in biopsies collected from uninfected subjects. Moreover, the frequencies of IFN-γ^+ and IL-17 A^+ cells are positively correlates with inflammation score but not with reduced bacterial colonization in the antrum of *H. pylori*-infected patient [101]. Another study in a mouse model with severe combined immunodeficiency has shown that transferring T cells derived from *H. pylori* infected patients into those mice induceed gastric ulcer, indicating that host immune system is involved in the progression of PUD [102].]. A study on mice infected with *H. felis* also demonstrated that neutralization of IFNγ significantly reduced inflammation in the stomach, strongly supporting the idea that preferential long-lasting activation of a Th1 cell responses contributes to maintenance and development of gastric pathology (Fig. 3). The magnitude of *H. felis*-induced gastric inflammation has been observed to be higher in mouse IL-$4^{-/-}$ than in their wild-type counterparts. Furthermore, infection with *H. felis* in BALB/c mice induced minimal gastric inflammation, whose genetic background is prone to high IL-4 production in response to various antigens of *H. felis* [84]. A recent study confirmed that the number of Treg cells and the expression of IL-10 and TGFβ1 were significantly lower in infected patients with PUD than in infected patients with gastritis [89]. The results offer further evidence that unlimited Th1 cell response is related to more severe gastroduodenal diseases (such as PUD and GC) in infected patients with *H. pylori*, whereas a mixed Th1/Th2 and Treg cells response is able to reduce the unbalanced Th1 cell responses and result in less severe pathological consequences [2,84,103].

7. Th1-cells and gastric cancer (GC)

GC is an important cause of mortality due to cancer and is estimated to be one of the most leading causes of all deaths worldwide. Although a number of factors are related to the development and progression of GC, a relationship with chronic gastric inflammation has become evident in recent years [104], the precise mechanism of the development of GC has not yet been elucidated [105]. In *H. pylori*-infection induced chronic gastritis mucosa, the number of T $CD4^+$ cells predominates over other cell types of the immune system [106]. T $CD4^+$ cells appear to be essential for the development of gastritis because gastritis does not develop in mice lacking T $CD4^+$ cells [76]. In addition, the development of gastritis by *H. pylori*-infection is impaired in IFN-γ-deficient mice, whereas IL-4 deficiency enhances the development of gastritis [79]. Therefore, IFN-γ produced by Th1 cells plays an important role in the development of gastritis. It has also been shown that those *H. pylori*-specific T cells are responsible for the infiltration of neutrophils and macrophage in the gastric mucosa [107]. In addition to the infiltration of T cells and activated neutrophils and macrophage cells, *H. pylori*-induced gastritis is characterized by the enhanced production of a variety of pro-inflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α have been reported to increase in *H. pylori*-infected patients [81,108,109], moreover, the major Th cells populations and their signature cytokines are suggested to play important roles in cancer development [110–112]. Chronic inflammation in infected patients with *H. pylori*

causes damage to the host gastric mucosa, cell proliferation and cytokine-induced DNA synthesis, hyperplasia and carcinogenesis [113], which make the gastric cancer become a long and complicated process. A recent study has shown that Th1 cell responses are expanded in GC tissue or in peripheral blood mononuclear cell populations, and mainly in lymph node metastasis of patients with GC. This data suggest that Th1 cells infiltration may contribute to the GC development and metastasis [114]. The studies using various mouse tumor models have supported a role of Th1 cell responses in antitumor immune responses. Th1 cell responses have been observed to exhibit a significant inhibitory function in the development of metastatic disease, but not in primary tumor in a mouse autochthonous prostate cancer model [115]. Th1 cell is required for adaptive immune responses against transplantable melanoma [116]. Surprisingly, Th1 (T-bet) deficiency has been reported to prevent *H. felis*-induced GC [117]. It was shown that Th1 (T-bet)-deficient mice respond to *H. felis* infection with a blunted Th1 response and a greatly reduced IL-1β and TNF-α but increased IL-10 levels. This result is, however, not contradictory to the idea that T-bet promotes antitumor immune responses. It is because in this case, the main role of T-bet is to facilitate *H. felis*-driven inflammation which precedes and is likely critical for gastric cancer development. Taken together, IFN-γ plays an important role in the control of *H. pylori* infection [118,119]. But, $CD4^+$ T cell-derived IFN-γ provides the key stimulus for development of gastric premalignant lesions that can progress to GC [118].

8. Conclusions

Activation of the different types of effector T cells influences the clinical outcome of *H. pylori* infection. *H. pylori* mediated immuopathology in gastric mucosal tissue of infected patients is associated with an inflammatory response with significant contribution of Th1-dominant cell responses. Virulence factors of *H. pylori* via activation of innate immune cells and release of inflammatory cytokines induce preferential development of *H. pylori*-specific Th1/Th17 cell responses. In this context increased Treg cell responses are capable of modulating Th1 and Th17 cell responses that possibly contributes to the persistence of *H. pylori*-infection and modulation of the tissue damage. Therefore, uncontrolled Th1/Th17 cell responses and the decrease of Treg cell responses in some infected patients might be associated with the development of more severe *H. pylori*-related diseases including PUD as a consequence of the induction of immunopathologic reactions. There are contradictory results in relation to the protective adaptive immunity of Th1/Th17 cell responses against *H. pylori* infection, which should be further investigated. Modulation of the effector $CD4^+$ T cells response to *H. pylori*-infection must be taken into consideration to design novel therapeutic strategies for the successful treatment of *H. pylori*-related complications.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.micpath.2018.06.033.

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